REMARKS

Claims 15-28 are pending in the application. Claims 19-22 and 24-28 have been withdrawn from the application. Claim 16 has been cancelled. Therefore, claims 15, 17, 18, and 23 are at issue.

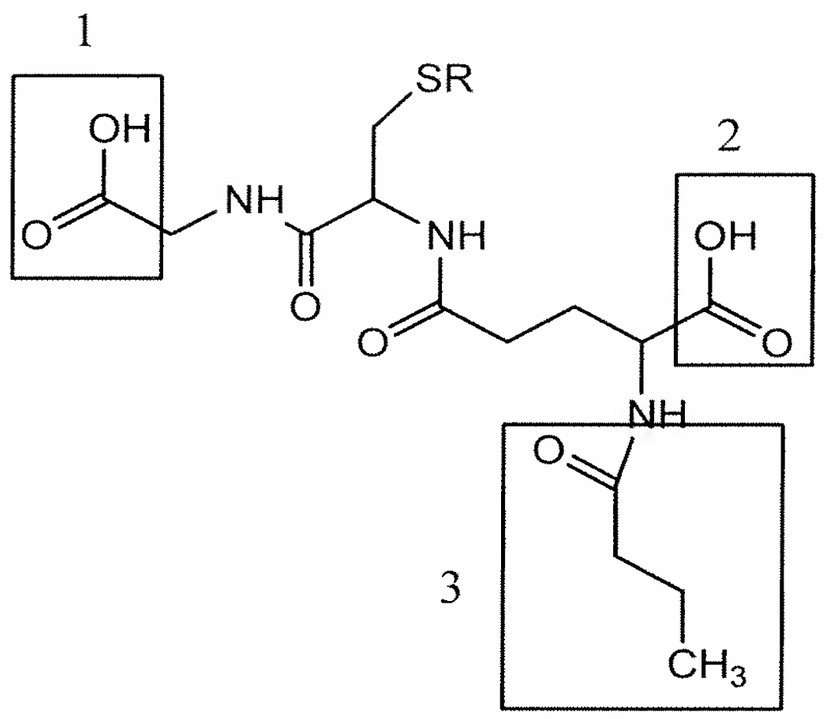
The specification has been amended to correct the structure of the glutathione derivative at page 1, lines 5-12. This amendment corrects an obvious typographical error and adds no new matter. In particular, the corrected structure includes an –OH group that was inadvertently omitted from the structure. The corrected structure is supported by the specification as a whole and in particular by the spectrum in Fig. 1 which contains the correct structure.

Independent claim 15 has been similarly amended, which also is supported by the specification and Fig. 1. Independent claim 15 also has been amended to incorporate the features of originally-filed and now cancelled claim 16.

Claims 15-18 and 23 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In response, claim 18 has been amended to correct the pendency of the claim. In addition, the structure of glutathione derivatives of claim 15 has been corrected, as discussed above. Accordingly, it is submitted that the rejection of claim 15, 17, 18, and 23 under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

Claims 15-18 and 23 stand rejected under 35 U.S.C. §103 as being obvious over Anderson et al. U.S. Patent No. 5,464,825 (‘825) in view of a McMurry publication (McMurry). The rejection is based on a contention that the ‘825 patent teaches alkyl monoesters of N-acyl glutathione to increase intracellular GSH leads, and that McMurry teaches ester hydrolysis. The examiner further relies upon an “obvious to try” rationale to support the rejection. Applicants traverse this rejection.

The present invention is directed to glutathione derivatives having a structure:



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wherein the features in highlighted boxes 1, 2, and 3 provide compounds that demonstrate unexpected benefits. In particular, the claimed compounds require both carboxyl groups of boxes 1 and 2 *and* the butanoyl group of box 3.

The '825 patent discloses N-acyl glutathione monoalkyl esters as depicted at column 4, lines 9-18. Although the '825 patent discloses increasing intracellular levels of GSH and GSH equivalents, this is accomplished by "administering an alkyl monoester of N-acyl glutathione, with the esterification occurring at the glycine carboxylic group" ('825 patent, column 3, lines 21-27). The present claims do not recite an ester group on the glycine residue, but require a carboxyl group.

The '825 patent also discloses that the alkyl R group of the glycine ester can contain 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms, with no apparent change in "GSH level elevating activity" (column 4, lines 33-43). In addition, the '825 patent discloses that the hydrocarbon portion of the acyl group, i.e., R^1, can contain 1-9 carbon atoms, and preferably 1-3 carbon atoms, also with no disclosed difference in GSH level elevating activity.

The '825 patent fails to teach or suggest using a glutathione derivative having two carboxyl groups and the butanoyl group of the present claims. The sole example of the '825 patent is N-acetyl glutathione monoethyl ester. In fact, the '825 patent teaches that the

monoester form is *necessary* to transport the molecule into the cells, i.e., '825 patent, column 7, line 56 through column 8, line 16 stating:

> "The findings disclosed herein indicate that *the administered N-acetyl GSH monoester is transported into* the cells of the liver and kidney where it is hydrolyzed to GSH; N-acetyl GSH and GSH monoester are also formed. The studies in which mice were pretreated with L-buthionine-SR-sulfoximine provide strong evidence for the transport of N-acetyl GSH monoesters; under these conditions, the synthesis of GSH from its constituent amino acids is markedly inhibited. Also the finding of N-acetyl GSH and GSH monoester in tissues is strong evidence that N-acetyl GSH monoester is transported into cells and hydrolyzed. It is *also seen that intact GSH is not delivered into the cell*, since GSH synthesis is markedly inhibited by L-buthionine-SR-sulfoximine. Thus, the present method permits increasing the intracellular GSH level in instances where a deficiency of the necessary synthetase for GSH exists, or where a higher level of GSH or N-acetyl GSH is beneficial." (emphasis added)

In contrast to the teachings of the '825 patent, the glutathione derivatives of claim 15 do not require an esterified glycine residue, but perform effectively when a carboxyl group is present on this residue. The glutathione derivative of claim 15 also requires the butanoyl group of box 3 to achieve the benefits of the present invention. The '825 patent provides no teaching or suggestion that a compound of the present invention having the features of boxes 1, 2, *and* 3 could enhance intracellular GSH levels.

As stated above, the presently claimed compounds do not rely solely upon a carboxyl group on the glycine residue for enhanced activity. The butanoyl residue of box 3 is important and necessary to achieve the enhanced activity of the present compounds. In particular, an acetyl group (2 carbons) is inactive and alkanoyl groups of other lengths are of low activity or are toxic (i.e., alkanoyl groups with eight and twelve carbons). See specification, page 6, lines 14-21 and page 11, line 22 through page 12, line 15. This is unexpected and in direct contrast to the teachings of the '825 patent, wherein the carbon length of the hydrocarbon group R^1 apparently does not effect compound activity, and the sole example is an acetyl group. Contrary to this teaching in the '825 patent, an acetyl group

in place of a claimed butanoyl group *destroys* the activity of the present compounds. This result could not have been predicted from the teachings of the '825 patent.

With respect to the examiner's reliance upon the '825 patent for teaching at column 4, line 21 to de-esterify the N-acetyl GSH monomer, first this is no more than a theory as set forth at column 5, lines 48-56 and column 7, line 56 through column 8, line 16. In addition, the sole example of an N-acyl GSH is N-acetyl GSH (see Example 1). Applicants have shown that N-acetyl GSH (referred to as GSH-C2 in the specification) *does not perform*, whereas the N-butanoyl GSH, as claimed and referred to as GSH-C4 in the specification, does perform. See specification, page 12, lines 8-15, for example.

With respect to the McMurry publication, this reference is merely a general teaching that esters can be hydrolyzed to acids. However, the primary '825 patent provides no incentive for a person skilled in the art to perform such a hydrolysis. In particular, the '825 patent specifically teaches that the *monoester* is required to achieved the benefits of the invention and that "intact GSH" (which contains two carboxyl groups) is not delivered into the cell ('825 patent, column 8, lines 9-12). This is further demonstrated in the examples of the '825 patent, wherein glutathione, having two carboxyl groups, "had only a slight effect" ('825 patent, column 7, lines 14-19).

To support the present obviousness rejection, the examiner relies upon an "obvious to try" rationale. To reject a claim based upon this rationale, the following must be articulated:

> "(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
>
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness."

If any of these findings cannot be made, then the "obvious to try" rationale cannot be used.

As stated in *Takeda Chemical Industries v. Alphapharm Pty. Ltd.*, 492 F3d. 1350, 1356-7 (2007):

> "That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."

The court then held that modifications to a prior art compound, including steps of homologation or ring-walking, did not render the new compounds obvious because nothing in the prior art provided a reasonable expectation that the modifications would be beneficial. Accordingly, even though the number of modifications were finite, the prior art failed to provide a reasonable expectation of success. The examiner also is directed to *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* 86 USPQ2d 1196 (Fed. Cir. 2008), for a discussion of the obvious-to-try rationale and avoiding hindsight analysis in deciding that a claimed compound would not have been obvious. Also, see *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008), wherein a compound having

ring substituent -$OCH_2CH_2CH_2OCH_3$ was found to be nonobvious over an identical prior art compound except for having a ring substituent of –OCH_2CF_3.

To arrive at the present invention, a skilled artisan would have to make modifications to the '825 compounds that are neither taught nor suggested by the '825 patent, but discouraged by the '825 patent teachings. In particular, the '825 patent specifically teaches the need for a monoester, and that GSH is not delivered to the cell. Accordingly, the '825 patent provides no reason for a chemist to modify a compound of the '825 patent in a way to arrive at the presently-claimed compounds.

Further, applicants found that the N-acetyl analog of the claimed compounds *did not* perform. Only the claimed N-butanoyl compounds demonstrated efficacy. In contrast, the N-acetyl *monoesters* of the '825 patent (see Example) perform well.

These findings further demonstrate the unexpected results provided by the present invention, which could not have been predicted from the disclosure of the '825 patent. The skilled person would have had *no* reasonable expectation of success if the proposed modifications resulting in the claimed compounds were made. It is the applicants who found that the specific butanoyl group (box 3), in combination with two carboxyl groups (boxes 1 and 2), are able to enter cells and provide efficacious results. Varying any of these moieties will reduce or destroy these efficacious results. In particular, chains shorter or longer than butanoyl are either ineffective or toxic. This discovery is in direct contrast to the '825 patent, which requires a monoester and suggests that all alkyl chain lengths are effective.

In summary, for all the reasons set forth above, it is submitted that claims 15, 17, 18, and 23 would not have been obvious under 35 U.S.C. §103 over a combination of the '825 patent and the McMurry publication, and that the rejection should be withdrawn.

It is further submitted that all claims are in a form for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

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Respectfully submitted,

By _____

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